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Original Article

A Population-based study of the Epidemiology of Chronic Hypoparathyroidism[†]

Short Title: Epidemiology of Hypoparathyroidism

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ABSTRACT

There are very few reports on the epidemiology of chronic hypoparathyroidism. A population-based study was undertaken to describe the prevalence and incidence of hypoparathyroidism in Tayside, Scotland. Data on biochemistry, hospital admissions, prescribing and death records in Tayside Scotland from 1988 to 2015 were linked electronically. Patients with at least three serum albumin corrected calcium concentrations below the reference range that were taken in an out-patient setting were included in the study. Patients with severe chronic kidney disease prior to low calcium were excluded from the study. Patients with hypocalcaemia were included if they had either previous neck surgery/irradiation, a low serum PTH or were treated with Vitamin D. Patients were identified as having either a post-surgical, a non-surgical cause, or had secondary hypoparathyroidism e.g. hypomagnesaemia. Overall 18,955 patients were identified with hypocalcaemia. Of these 222 patients had primary hypoparathyroidism, 116 with post-surgical and 106 with non-surgical chronic hypoparathyroidism. In 2015 the prevalence of primary hypoparathyroidism was 40 per 100,000, with a rate of 23 and 17 per 100,000 respectively for post-surgical and non-surgical. 80% of the former and 64% of the latter were female. The mean serum calcium at diagnosis was 1.82mmol/l (SD \pm 0.24) and the annual incidence varied from 1-4 per 100,000. Overall, 71% of patients were prescribed Vitamin D and/or calcium, whilst activated Vitamin D was used in 48% of post-surgical cases and 43% of non-surgical cases. Thyroxine and/or hydrocortisone were prescribed in over 90% of post-surgical and 64% of non-surgical cases. In conclusion, the prevalence of non-surgical chronic hypoparathyroidism was greater than previously reported using this population-based approach. Many had mild hypocalcaemia and did not receive any treatment. This article is protected by copyright. All rights reserved

Key words: General population study, epidemiology, Parathyroid-related disorders, Health Services Research, Statistical Methods

INTRODUCTION

Hypoparathyroidism is a rare condition that may present with a range of symptoms from having no symptoms to life threatening hypocalcaemia (1,2). Symptoms are broadly related to the severity of hypocalcaemia. Hypoparathyroidism may be transient, such as after neck surgery, or may be chronic. Chronic hypoparathyroidism can result from permanent damage to the parathyroid glands from surgery or radiotherapy and is closely related to the number of parathyroid glands remaining after surgery (3). Autoimmunity and rare genetic conditions may also cause hypoparathyroidism, but many cases remain idiopathic (4). Hypoparathyroidism can be due to other correctable causes including hypomagnesaemia, which can be treated with magnesium replacement. Not all patients require treatment, such as those with mild hypocalcaemia. For those who do require therapy, this is usually in the form of activated vitamin D analogues, such as 1-alpha calcidol or calcitriol, with or without calcium tablets. Traditionally, the aim of treatment has been to maintain the serum calcium level around the lower limit of the reference range, to limit the risks of hypercalciuria and hypercalcaemia with the resultant risks of symptoms, renal stones, and other complications. Treatment may become more straightforward with the introduction of parathyroid hormone as a substitute therapy.

Post-surgical hypoparathyroidism is the commonest cause of hypoparathyroidism, occurring in 25 - 60% of surgical neck explorations (4-6). However, the majority are transient cases, with 70% resolving after 2 months, 90% at 6 months and possibly as few as 2-5% persist at one year (5,7). In Denmark, the prevalence of hypoparathyroidism was studied using the national hospital contact disease register linked to prescribing records (8,9). The overall prevalence was around 24 per 100,000 people, with rates of 22 per 100,000 chronic post surgical cases (9) and 2.3 per 100,000 non-surgical cases (8). There was a female predominance of around 88% in post-surgical hypoparathyroidism (9), but only 53% in non-surgical cases (9). The average age was 49 and 50 years respectively. The annual incidence

of cases was around 0.8 per 100,000 people (9), with an incidence of about 0.1 per 100,000 of autoimmune hypoparathyroidism (10). Interestingly around 4% of people were treated with magnesium (9).

Another study in Norway using hospital registry reported that the prevalence of hypoparathyroidism was lower at 10.2 per 100,000 (11), but this reflected a lower proportion of post-surgical cases at 6.4 per 100,000, and a higher rate of non-surgical cases of 3.0 per 100,000. An estimated prevalence of hypoparathyroidism of around 37 per 100,000 in the US has been reported in an abstract (12,13), with a rate of 8 per 100,000 non-surgical cases. From a further US study based on a health care claims database and a market-based research study, an approximate prevalence of 25 cases per 100,000 was estimated (5). Further studies have demonstrated a prevalence of hospitalisations due to hypoparathyroidism of 5.9 per 100,000 (14) and idiopathic hypoparathyroidism of 0.7 to 0.9 per 100,000 (15,16). The latter two studies were pre-2000 and it is difficult to know if rates have increased or whether ascertainment has improved.

Most of these studies rely on hospital based records with prescribing data in a proportion of studies. As primary care records were not included it is possible some cases may have been missed, especially milder non-surgical related cases that may not even have needed treatment. We were able to link hospital records with primary care information, prescribing and biochemistry records to identify cases with chronic hypoparathyroidism. We aimed to describe the epidemiology of chronic hypoparathyroidism using this population-based dataset in Tayside, Scotland.

METHODS

Patients

All patients registered with a General Practitioner in Tayside are issued with a unique ten digit patient identification code which has been used for all healthcare activity since 1979. All such records are held at the Health Informatics Centre and linked anonymously for healthcare research (HIC, <http://www.dundee.ac.uk/hic>) at the University of Dundee. The study was approved by the Tayside Medical Ethics Committee and data protection by the Tayside Caldicott Guardians. All analyses were performed on anonymised datasets. The following datasets were linked: biochemistry, hospital admission (Scottish Morbidity Records (SMR)), drug prescribing records, death and patient migration (General Registry Office).

a) Primary analysis

All patients of 18 years and over who had a low serum calcium concentration recorded on at least three occasions more than one month apart ($\leq 2.15\text{mmol/L}$) were identified from the biochemistry dataset in Tayside. All serum calcium concentrations mentioned in this study were corrected for albumin concentration. Only recordings undertaken as outpatients were included in this study because many inpatients have transient hypocalcaemia. Patients who in addition also had at least one of the following criteria were classified as potentially having hypoparathyroidism:

1. Evidence of previous neck surgery or irradiation prior to hypocalcaemia or admission with hypoparathyroidism. Data was collected from SMR and operation procedures.
 - a. OPCS codes: B08, B09, B12, B14, E29.8, E29.9, E30, E31, E34, E35, E38

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- b. ICD10 codes: D02.0, C32.0, C32.1, C32.2, C32.3, C32.8, C32.9, C73, Z85.21, Z85.850
 - c. ICD9 codes: 231.0, 161.0, 161.1, 161.2, 161.3, 161.8, 161.9, 193, v10.21, v10.87
 - d. ICD 9/10 codes for hypoparathyroidism: 252.1, E20.8, E20.9, E82.1 and E89.2.
2. Low or inappropriately normal plasma parathyroid hormone (PTH) while having low calcium (within 4 months) – PTH \leq 5pmol/L or 50ng/L (reference range 1-6.9 pmol/L). Data was collected from Biochemistry.
 3. On long term treatment with Calcium (BNF code: 9.5.1.1) and/or any Vitamin D (BNF code: 9.6.4) drugs – at least 3 prescriptions in a year. Data was collected from prescribing dataset.

Patients were excluded based on the following criteria (see Figure 1):

1. Patients who had high serum PTH (>7 pmol/L) while having low calcium (within 4 months), as this represents secondary hyperparathyroidism and not primary hypoparathyroidism.
2. Patients who had low Vitamin D while having low calcium (within 4 months) in the absence of a low serum PTH, as this was most likely to represent secondary hyperparathyroidism and not primary hypoparathyroidism.
3. Patients who had less than three low calcium levels after excluding calcium measurements taken during admission. Patients with hypocalcaemia whilst being in the hospital may be due to malnutrition and critical illness and is thus unrelated to chronic parathyroid disease.
4. Patients who had low calcium concentrations as an outpatient, but all within 1 month of each other, as this did not represent sustained hypocalcaemia and was likely to be transient disease.

5. Use of bisphosphonates and denosumab (BNF code: 6.6.2) within 6 months prior to low calcium measurement.

Therefore, patients would have had at least three low serum calcium concentrations undertaken as an outpatient at least one month apart were included in this study. These criteria are likely to exclude all patients with transient hypocalcaemia, but in addition the percentage of patients with a low serum calcium concentration recorded more than 3 and 6 months apart was measured.

Patients who met all the criteria above were then categorised into three groups to help to confirm the cause of hypoparathyroidism based on the criteria below (see figure 1):

1. Evidence of previous neck surgery or irradiation prior to hypocalcaemia
2. Low magnesium levels within 3 months of having low calcium.
3. Uncategorised with a normal serum magnesium concentration (or no record of serum magnesium) within 3 months of having low calcium.

b) Secondary Analysis

Based on the primary analysis, the patients in the uncategorised group were defined as having 'non-surgical hypoparathyroidism' if they met any of the following criteria. The rest of the uncategorised patients were excluded from the cohort (see Figure 1).

1. Patients who always had $PTH \leq 5 \text{ pmol/L}$, at least one within 4 months of low serum calcium and were on alfacalcidol or calcitriol, or had an inpatient admission recorded as hypoparathyroidism

2. Patients who always had PTH ≤ 5 pmol/L within 4 months of having low serum calcium but were not on alfacalcidol or calcitriol
3. Patients who did not have any PTH recording during the study period but were on alfacalcidol/calcitriol
4. Patients who did not have any PTH recording during the study period, were not on activated Vitamin D but were on hydrocortisone or/and thyroxine

Finally patients who had an eGFR <20 or creatinine $> 200 \mu\text{mol/L}$ prior or on the day of the first low serum calcium were excluded from the study (all subgroups). These patients are most likely to be hypocalcaemic and on activated Vitamin D as a result of chronic kidney disease as the renal failure predated the hypocalcaemia. The main reason other patients were excluded was because they had no serum PTH assay, were not on activated Vitamin D, hydrocortisone nor thyroxine

c) Prevalence and incidence rates

The yearly and 5 yearly prevalence and incidence rates were calculated for the whole cohort that included those with post-surgical hypoparathyroidism, non-surgical hypoparathyroidism and hypoparathyroidism secondary to hypomagnesaemia. Estimates were also calculated for post-surgical and non-surgical groups separately.

RESULTS:

After applying the inclusion and exclusion criteria, a total of 280 patients were identified (Figure 1). There were 116 patients in the post-surgical cohort, 106 patients in the idiopathic non-post-surgical cohort and 58 with secondary hypoparathyroidism due to hypomagnesaemia.

The median duration of follow up was 107 months for all patients and 116 months for patients with post-surgical or non-surgical primary hypoparathyroidism. Classification of patients from the idiopathic non-surgical group into four subgroups is illustrated in Figure 2. The baseline characteristics of these patients are illustrated in Tables 1 and 2. Patients with hypomagnesaemia were older and less likely to be treated with activated Vitamin D preparations compared to patients in the post-surgical and idiopathic non-surgical groups

Of all patients in our cohort, 88.2% (n=247) had low serum calcium measurements more than 3 months apart and 79.3% (n=222) had them more than 6 months apart. This figure increases to 83% for a 6 months duration if all serum calcium recordings are included i.e. in-patient and out-patient. In the non-surgical group, 85% of the patients had hypocalcaemia for 6 months or longer. Overall 59.1% of patients with hypoparathyroidism had a serum PTH checked.

The post-surgical group had a higher proportion of females, and a lower nadir plasma PTH concentration than the idiopathic non-surgical cases (Table 1). Within the latter group, those not treated with activated Vitamin D had higher nadir serum calcium and PTH concentrations, suggestive of milder disease, than other non-surgical hypoparathyroid cases (Table 2). A large proportion of the non-surgical cases (64%) and the hypomagnesaemia cases (69%) were on hydrocortisone and/or thyroxine, suggestive of a possible ongoing autoimmune process.

Severity of disease was assessed by measuring the lowest ever concentration of serum calcium for the post-surgical and non-surgical patients. For post-surgical and non-surgical cases respectively, the proportion of patients with the lowest recorded serum calcium below 2.1 mmol/l were 93.1% and 95.3%, serum calcium below 2.0mmol/l were 75.9% and 59.4% and a serum calcium below 1.8 mmol/l were 44.8% and 31.1%. For patients treated with activated Vitamin D (n=118) the proportion who subsequently developed a serum calcium <1.85 mmol/l was 6.8%, who developed a serum calcium >2.55mmol/l was 1.7% and who developed a serum phosphate >1.5 mmol/l was 22.0%.

The prevalence and incidence rates for the whole cohort, post-surgical and idiopathic non-surgical is illustrated in yearly and 5-yearly bands in Tables 3 and 4. In 2015, the prevalence rate for the whole cohort was 47 per 100,000 people and 40 per 100,000 for the combined endpoint of post-surgical (23 per 100,000) and non-surgical patients (17 per 100,000).

As a sensitivity analysis we re-calculated the prevalence for 2015 after excluding all patients who a) had low serum calcium concentrations less than 6 months or b) had a low serum albumin concentration and a serum PTH >1.6 pmol/L. It could be argued that the latter group had malabsorption as their cause for hypocalcaemia. After excluding these groups the overall prevalence for the combined endpoint of post-surgical and non-surgical hypoparathyroidism was 32 per 100,000 with rates of post-surgical and non-surgical hypoparathyroidism being 18 and 14 per 100,000 respectively.

DISCUSSION

We estimated the prevalence of endogenous chronic hypoparathyroidism in 2015 to be 40 per 100,000 which is similar to the rate observed in the US at 37 per 100,000 (12) but greater than that seen in other European studies at 10-24 per 100,000 (8, 9, 11). Our prevalence of 23 per 100,000 of the population for post surgical hypoparathyroidism is broadly similar to most other estimates from Europe, and the US at 22 to 29 per 100,000 (9,12,13).

Our prevalence of 17 per 100,000 for non-surgical hypoparathyroidism however is significantly greater than previous estimates of non-surgical hypoparathyroidism, where rates of around 2-3 per 100,000 in Denmark, and Norway (8,11) have been reported. In the US study, the non-surgical prevalence was 8 per 100,000 (12,13). In our non-surgical cohort, only 71% of patients were on calcium or Vitamin D, indicating that a number of patients had mild hypocalcaemia not noticed or not deemed to require calcium replacement. Two thirds of patients in the non-surgical group were on hydrocortisone and/or thyroxine suggestive of a history of autoimmunity, a common cause of non-surgical hypoparathyroidism. This is indicative that many patients had an autoimmune condition, increasing the likelihood of hypoparathyroidism. Unfortunately we did not have access to immunology data for auto-antibody results. There will be a number of reasons why only 59% of patients had a recording of plasma PTH. Many of these patients may not have had a formal diagnosis of hypoparathyroidism, with results being missed, ignored or judged as irrelevant and not needing treatment by clinicians. Such patients may not have been referred for specialist opinions – especially in non-surgical cases. There may also have been problems with data-linkage or lack of availability of PTH assays before they became widely available (e.g. in the 1980s).

When patients with hypocalcaemia for less than 6 months and those in whom it could be argued may have malabsorption (low albumin, low calcium and inappropriately normal PTH) were

excluded, the rate of hypoparathyroidism fell from 40 to 32 per 100,000 with rates of 18 and 14 per 100,000 in the post-surgical and non-surgical groups respectively. This still indicates a post-surgical prevalence similar to the literature but the non-surgical prevalence remains significantly greater than previously reported.

The higher proportion of non-surgical patients identified in our study may be due to the method used. In this study patients were identified using biochemistry records in primary and secondary care, which were linked and augmented by hospital registrations and prescribing records. Previous studies have been mainly based on patient registrations and/or prescribing. It is likely that most post-surgical cases would have been seen and registered in a hospital clinic, as reflected by the similar prevalence between the current study and previous ones. However, it is to be expected that our methodology would identify patients who were not identified in previous studies. Our methodology would identify patients that fit the criteria for hypoparathyroidism but have not previously been recognised and/ or not been referred to a specialist and/or not placed on a register or inappropriately removed from a database. It is likely that the additional patients that we identified would have less severe disease that did not necessitate hospital care, or even drug treatment. All our patients had three serum calcium concentrations below 2.15 mmol/L in an out-patient setting and 94% had a serum calcium less than 2.10 mmol/L. Thus, a small number of patients (~6%) had marginal hypocalcaemia which may not have been of clinical significance. In some other cohorts, it seems that virtually all patients were on activated Vitamin D (11), whilst 25% of our overall cohort did not require regular calcium and/or Vitamin D treatment, again suggesting milder disease in our cohort. Although some of the patients we identified had mild biochemical abnormalities, we cannot comment on the severity of their symptoms or quality of life.

In our analysis, approximately 60% of people with non-surgical hypoparathyroidism were likely to have had autoimmune disease, as judged by co-prescribing of thyroxine and/or hydrocortisone, which is higher than the 17% reported by Astor (11). Unfortunately, we did not have robust data on genetic causes, but previous studies have estimated genetic causes to be 31-38% of all non-surgical (living) cases (15, 16), with the commonest being CASR gene mutations, Di-George syndrome and HDR syndrome (hypoparathyroidism, deafness and renal abnormalities). If this figure were applicable to our population this would leave approximately 10% as genuinely idiopathic.

The annual incidence of non-surgical hypoparathyroidism was generally around 1-4 per 100,000 of the general population but did vary quite considerably from year to year. The rate is higher than the only other reported incidence we could identify from Denmark of 0.8 per 100,000 (9). Although this may reflect methodological differences explained above there are very few studies reporting the incidence of hypoparathyroidism.

There are a number of possible reasons for regional variation in the rates of hypoparathyroidism. Post-surgical hypoparathyroidism will reflect the amount of thyroid surgery being undertaken, which will partly reflect different and changing practices in the use of radioactive iodine for benign thyroid disease. Locally, surgery for benign thyroid disease has decreased (17) and this may explain the declining post-surgical incidence of hypoparathyroidism. Also the rates of chronic post-surgical hypoparathyroidism between centres appear to vary significantly possibly from 1 to 15% (18). Non-surgical hypoparathyroidism has a strong genetic aetiology, and it is likely that there will be “pockets” of disease reflecting clusters of genetic abnormalities. It is also known that autoimmune diseases have geographical clustering, all of which will affect the prevalence of hypoparathyroidism.

Further analysis of the subgroups of idiopathic non-surgical hypoparathyroidism (Figure 2) is of interest. It should be remembered that all these patients had chronic hypocalcaemia from samples taken when not in hospital. Group 1 had very strong criteria that match a diagnosis of hypoparathyroidism – as they had a low or inappropriately normal PTH concentration and were on activated Vitamin D, or had an ICD code for hypoparathyroidism. Group 2 are highly likely to have hypoparathyroidism, but it is likely that many had longstanding disease dating back to a time when PTH assays were less easily accessed and less reliably recorded. These patients had chronic hypocalcaemia and were on activated Vitamin D and did not have renal failure at baseline. Group 2 and 4 both had very high rates of co-prescribing thyroxine and/or hydrocortisone consistent with previous neck surgery or having a poly-endocrinopathy. Even in group 3 where patients fitted the biochemical criteria for diagnosis but were not taking activated Vitamin D, 50% were co-prescribed thyroxine and/or hydrocortisone. As discussed it is likely that many of this group had mild hypocalcaemia as reflected by a higher nadir serum calcium and a lower prescribing rate for calcium replacement therapies (Table 2). These however are the type of patient who are easily missed in epidemiological studies.

The strength of our study is that it is population-based and will include review of anyone who has had contact with a healthcare professional in primary and secondary care. We used an algorithm which will have identified patients missed by other studies but it is possible that we may have misclassified some patients with transient disease as having chronic hypoparathyroidism. We tried to limit this by only including serum calcium collections undertaken more than 4 weeks apart and taken as an outpatient, as most transient hypocalcaemia occurs in inpatients. In addition, 88% of patients had low serum calcium measurements more than 3 months apart and 83% more than 6 months apart by which time many patients would have been established on replacement treatment. We may have failed to identify some cases as post-surgical if there were coding inaccuracies. However our overall

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post-surgical prevalence rate is similar to other reports and therefore the high rate of non-surgical cases we identified is more likely to be genuine and reflect the population-based methodology. We have not included patients with pseudohypoparathyroidism. It is likely that our calculated prevalence of hypoparathyroidism is an underestimate as we were quite stringent about excluding cases in whom we were not confident about the diagnosis, and some cases may have been missed using our methodology. When patients were identified using only ICD codes for hypoparathyroidism, only three patients (~1%) who would not have been identified from other combined sources using the algorithm were identified. This suggests the algorithm used to identify patients was fairly robust. It is possible that we over-diagnosed some cases on non-surgical hypoparathyroidism. However a sensitivity analysis which removed cases with low calcium less than 6 months or people with possible malabsorption as a cause of the hypocalcaemia indicated a prevalence rate of non-surgical hypoparathyroidism that remained well above the reported literature. It would have been ideal if we could have looked at the causes of the non-surgical cases in more detail, and identify genetic, autoimmune and infiltrative causes, but the data was insufficient to allow such a detailed analysis. Serum calcium concentrations were always corrected for albumin concentration in this study. Although estimations of ionised calcium concentrations would have been preferable, this is not done as part of routine practice in most UK Laboratories.

In summary, the current study describes the epidemiology of chronic hypoparathyroidism using a different methodology to that used in the published literature, which is population-based. The rate of post-surgical hypoparathyroidism was 23 per 100,000 which is similar to previous reports, but the prevalence of non-surgical hypoparathyroidism was 17 per 100,000 which is 2-6-fold higher than reported before, although many of these patients had mild hypocalcaemia and some did not need activated Vitamin D treatment.

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Authors' roles: Study design: TV, PD and GL. Data analysis: TV. Data interpretation: TV and GL. Drafting manuscript: TV and GL. Revising manuscript content: TV, PD and GL. Approving final version of manuscript: TV, PD and GL. TV takes responsibility for the integrity of the data analysis.

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REFERENCES

1. Cusano NE, Rubin MR, Bilezikian JP. Parathyroid hormone therapy for hypoparathyroidism. *Best Pract Res Clin Endocrinol Metab.* 2015; 29; 47-55
2. Shoback D. Clinical practice. Hypoparathyroidism. *NEJM* 2008; 359: 391-403
3. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A. Importance of in situ preservation of parathyroid glands during total thyroidectomy. *Br j Surg* 2015; 102: 359-367
4. Bollerslev J, Rejnmark L, Marcocci C, Shoback DM, Sitges-Serra A, van Biesen W, Dekkers OM European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. *Eur J Endocrinol.* 2015;173:G1-20.
5. Powers J, Joy K, Ruscio A, Lagast H. Prevalence and incidence of hypoparathyroidism in the United States using a large claims database. *J Bone Miner Res.* 2013;28:2570-6.
6. Page C, Strunski V. Parathyroid risk in total thyroidectomy for bilateral, benign, multinodular goitre: report of 351 surgical cases. *J Laryngol Otol.* 2007;121:237-41.
7. Ritter K, Elfenbein D, Schneider DF, Chen H, Sippel RS. Hypoparathyroidism after total thyroidectomy: incidence and resolution. *J Surg Res* 2015; 197: 348-353
8. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. The Epidemiology of Nonsurgical Hypoparathyroidism in Denmark: A Nationwide Case Finding Study. *J Bone Miner Res.* 2015; 30:1738-44.
9. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Cardiovascular and renal complications to postsurgical hypoparathyroidism: a Danish nationwide controlled historic follow-up study. *J Bone Miner Res.* 2013;28:2277-85.
10. Betterle C, Garelli S, Presotto F. Diagnosis and classification of autoimmune parathyroid disease. *Autoimmun Rev.* 2014;13:417-22.
11. Astor MC, Løvås K, Debowska A, Eriksen EF, Evang JA, Fossum C, Fougner KJ, Holte SE, Lima K, Moe RB, Myhre AG, Kemp EH, Nedrebø BG, Svartberg J, Husebye ES.

Epidemiology and Health-Related Quality of Life in Hypoparathyroidism in Norway. *J Clin Endocrinol Metab.* 2016; 101:3045-53.

12. Clarke BL, Leibson C, Emerson J, Ransom JE, Lagast H. Co-morbid medical conditions associated with prevalent hypoparathyroidism: a population-based study [abstract SA0170]. *J Bone Miner Res.* 2011;26:S182.

13. Clarke BL, Brown EM, Collins MT, Jüppner H, Lakatos P, Levine MA, Mannstadt MM, Bilezikian JP, Romanischn AF, Thakker RV. Epidemiology and Diagnosis of Hypoparathyroidism. *J Clin Endocrinol Metab.* 2016;101:2284-99.

14. Cipriani C, Pepe J, Biamonte F, Manai R, Biondi P, Nieddu L, Cianferotti L, Briandi ML, Minisola S. The epidemiology of hypoparathyroidism in Italy: An 8-year register-based study. *Calcif Tissue Int* 2017; 100: 278-285

15. Nakamura Y, Matsumoto T, Tamakoshi A, Kawamura T, Seino Y, Kasuga M, Yanagawa H, Ohno Y. Prevalence of idiopathic hypoparathyroidism and pseudohypoparathyroidism in Japan. *J Epidemiol.* 2000;10:29-33.

16. Zlotogora J, Cohen T. Idiopathic hypoparathyroidism in Israel. *Isr J Med Sci.* 1981;17:53-4.

17. Smith DM, Dutta S, Ahmed F, Thaha MA. Change in Practice over Four Decades in the Management of Graves' Disease in Scotland. *J Thyroid Res.* 2016;2016:9697849.

18. Stack BC, Bimston DN, Bodenner DL, Brett EM, Dralle H, Orloff LA, Pallota J, Snyder SK, Wong RJ, Randolph GW. (2015) American Association of Clinical Endocrinologists and American College of Endocrinology Disease state clinical review: Postoperative hypoparathyroidism – definitions and management. *Endocrine Practice* 2015; 6; 674-685.

FIGURE LEGENDS:

Figure 1: Pathway used to identify patients with hypoparathyroidism

Figure 2: Classification of Idiopathic non-surgical cases

Table 1: Baseline characteristics

Variables	Cohort	Sub-cohort		
		Post-Surgical	Non-surgical	Hypomagnesaemia
N (%)	280	116 (41.4)	106 (37.9)	58 (20.7)
Gender – Male, n (%)	86 (30.7)	23 (19.8)	38 (35.8)	25 (43.1)
Age, mean (SD)	51.6 (19.3)	47.1 (19.9)	50.5 (17.9)	62.8 (16.1)
Lowest Calcium, mean (SD)	1.82 (0.24)	1.83 (0.20)	1.88 (0.22)	1.70 (0.30)
Lowest PTH, mean (SD)	1.80 (1.53)	1.12 (1.06)	2.19 (1.65)	1.85 (1.52)
On Vitamin D or calcium (%)	212 (75.7)	82 (70.7)	75 (70.8)	55 (94.8)
Alfacalcidol/calcitriol, n (%)	118 (42.1)	56 (48.3)	45 (42.5)	17 (29.3)
Thyroxine/hydrocortisone, n (%)	213 (76.1)	105 (90.5)	68 (64.2)	40 (69.0)

Table 2: Baseline characteristics – for the idiopathic non-surgical group

Variable	Group 1	Group 2	Group 3	Group 4
N (%)	24	22	49	11
Gender – Male, n (%)	9 (37.5)	8 (36.4)	16 (32.7)	5 (45.5)
Age, mean (SD)	48.7 (20.2)	53 (16.5)	47.6 (17.2)	62 (14.9)
Lowest Calcium, mean (SD)	1.62 (0.23)	1.87 (0.17)	1.97 (0.13)	2.03 (0.05)
Lowest PTH, mean (SD)	0.79 (0.84)	-	2.88 (1.51)	-
Alfacalcidol/calcitriol, n (%)	23 (95.8)	22 (100.0)	-	-
Thyroxine/hydrocortisone, n (%)	15 (62.5)	17 (77.3)	25 (51.0)	11 (100.0)

Group 1: Patients who always had PTH \leq 5pmol/L and were on alfacalcidol or calcitriol and who were identified through ICD codes in the admission record

Group 2: Patients who did not have any PTH recording but were on alfacalcidol or calcitriol

Group 3: Patients who always had PTH \leq 5pmol/L and had low or inappropriately normal PTH while having low calcium (within 4 months) but were not on alfacalcidol or calcitriol

Group 4: Patients who did not have any PTH recording and were not on activated Vitamin D but were on hydrocortisone or/and thyroxine

Table 3: Yearly prevalence and incidence rate of hypoparathyroidism

Year	Prevalence rate (%)			Incidence rate (per 100,000 population)		
	Cohort	Surgical cohort	Idiopathic non-surgical cohort	Cohort	Surgical cohort	Idiopathic non-surgical cohort
1988	0.002	0.000	0.002	1.802	0.000	1.802
1989	0.005	0.001	0.004	3.609	0.773	2.578
1990	0.008	0.001	0.006	2.307	0.513	1.282
1991	0.011	0.003	0.007	3.833	1.789	1.533
1992	0.016	0.004	0.009	4.313	1.269	1.522
1993	0.019	0.006	0.010	3.793	2.276	1.264
1994	0.023	0.008	0.011	5.051	2.020	1.515
1995	0.028	0.009	0.013	5.790	1.259	3.273
1996	0.029	0.010	0.013	0.758	0.253	0.253
1997	0.028	0.009	0.013	0.253	0.000	0.253
1998	0.027	0.009	0.013	0.508	0.254	0.254
1999	0.027	0.010	0.012	1.019	0.509	0.255
2000	0.027	0.010	0.012	0.512	0.512	0.000
2001	0.028	0.011	0.012	2.058	1.543	0.257
2002	0.029	0.012	0.012	1.288	1.030	0.258
2003	0.031	0.014	0.012	2.573	1.544	0.257
2004	0.032	0.015	0.012	1.794	1.025	0.000
2005	0.032	0.015	0.012	0.763	0.254	0.509
2006	0.033	0.016	0.012	1.771	1.012	0.253
2007	0.034	0.017	0.012	1.757	1.255	0.502
2008	0.036	0.018	0.013	2.986	0.995	1.493
2009	0.039	0.020	0.013	4.204	2.226	0.989
2010	0.040	0.020	0.013	2.948	1.474	0.491
2011	0.043	0.021	0.015	3.413	1.463	1.463
2012	0.047	0.023	0.017	4.857	1.214	2.429
2013	0.049	0.024	0.017	3.154	1.456	1.213
2014	0.048	0.024	0.017	2.175	0.725	0.483
2015	0.047	0.023	0.017	0.723	0.482	0.241

Table 4: Prevalence and incidence of hypoparathyroidism – 5 year block

Year	Prevalence rate (%)			Incidence rate (per 100,000 population)		
	Cohort	Surgical cohort	Idiopathic non-surgical cohort	Cohort	Surgical cohort	Idiopathic non-surgical cohort
1990-1994	0.025	0.009	0.011	19.282	7.865	7.104
1995-1999	0.031	0.010	0.014	8.347	2.277	4.300
2000-2004	0.035	0.015	0.013	8.241	5.666	0.773
2005-2009	0.042	0.020	0.015	11.547	5.773	3.765
2010-2014	0.053	0.025	0.019	16.515	6.315	6.072

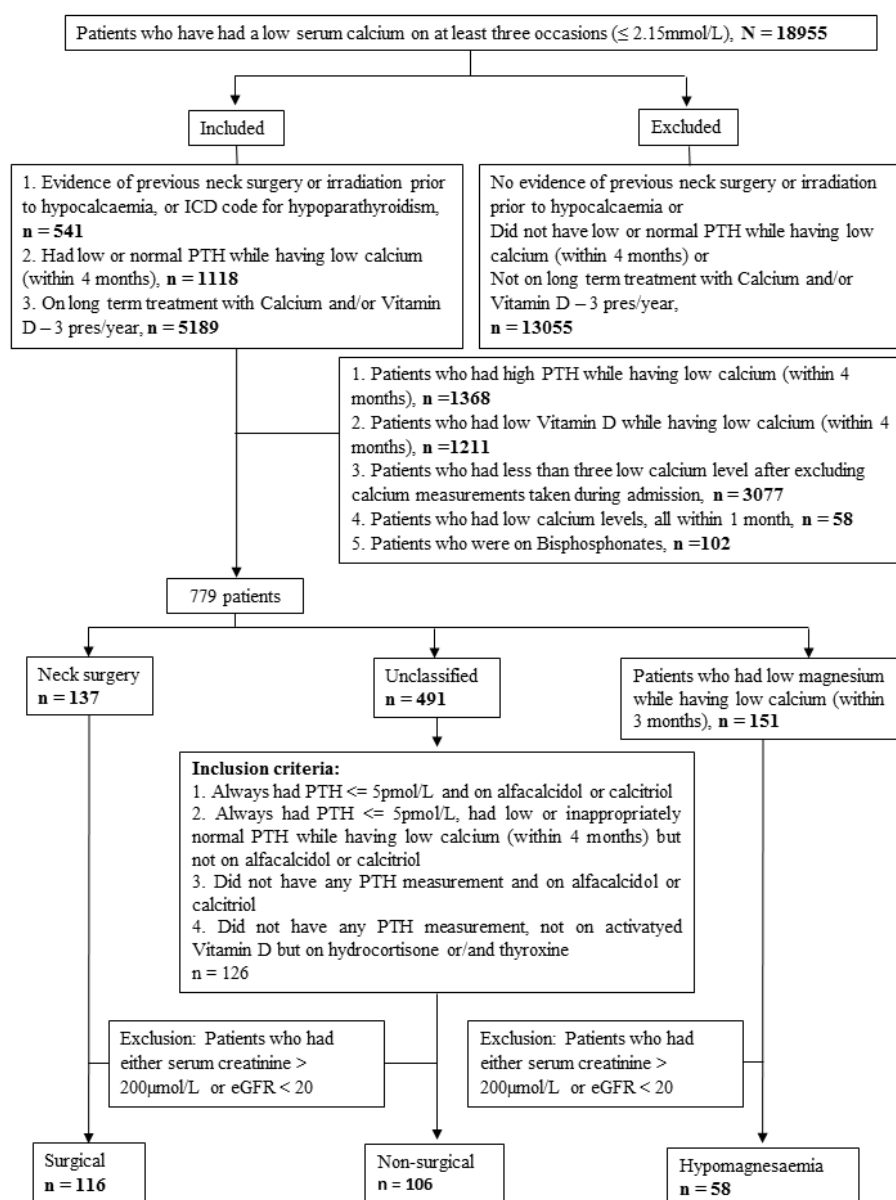
Figure 1

Figure 2